REMARKS

At the outset, Applicant acknowledges that the case is hereby reopened. Applicant wishes to thank the Examiner for the courtesy of a teleconference on January 19, 2006, wherein clarification regarding the present status of claims 36-37 was provided. Applicant also acknowledges the courtesy extended by the Examiner in granting a teleconference on January 23, 2006, wherein certain of the rejections were discussed in the context of experimental evidence presented in the specification.

In accordance with the Office Action, claims 34-38 are currently under examination. In view of the above, it is Applicant's understanding that claims 36-37 are pending and are designated herein as "currently amended". Claims 40-41 remain withdrawn. Claims 1-18 and 39 were previously canceled. Claims 19-33 and 40-41 are canceled herein without prejudice. Claims 35-38 are amended herein to more clearly define terms recited therein. New claims 42 and 43 are presented herein. Accordingly, claim 34, claims 35-38, as amended, and new claims 42-43 are under consideration.

Any amendment, however, is not to be construed as abandonment of any subject matter of the originally filed application. Accordingly, it is to be understood that Applicant reserves the right to reintroduce subject matter deleted from the application by the foregoing amendments and to file one or more divisional, continuation, and/or continuation in part applications directed to such subject matter.

Support for the amendments to the claims is found throughout the specification and in the original claims. Support for amendment to claims 35-38 is found in previously presented claims 35-38. Support for new claims 42 and 43 is found, for example, at page 8, line 12 through to page 9, line 21 and at page 15, lines 8-14. No issue of new matter is introduced by these amendments.

Rejections under 35 USC § 112

Claims 34-38 have been rejected under 35 USC § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. In view of Applicant's arguments, the rejection, as it applied to claims 34-38, is respectfully traversed.

The Examiner maintains that the specification has allegedly not enabled the scope of the claimed invention because the claims encompass *in vivo* or *ex vivo* gene therapy, for which the state of the art is such that it is allegedly unpredictable whether the claimed chimeric receptor can be used for such purposes. The Examiner does, however, appear to acknowledge that the state of the art is predictable with respect to instances wherein CTL that are capable of effecting a therapeutic response on their own are transduced or transfected *ex vivo* with a nucleic acid sequence and then adoptively transferred. Applicant confirms that the *in vivo* efficacy of a variety of cell*s* transfected *ex vivo* had already been demonstrated prior to the time of filing of the present invention. This statement is corroborated by at least three references cited in the specification at page 2, namely Moritz et al. (1994, Proc. Natl. Acad. Sci. 91:4318-4322), Hwu et al. (1995, Cancer Res. 55:3369-3373), and Hekele et al. (1996, Int. J. Cancer 68:232-238). Copies of these references are submitted for the Examiner's consideration and are listed as references AJ-AL on the Supplemental Information Disclosure Statement attached herewith.

In accordance with the Examiner's assertions regarding a cell that is capable of effecting a therapeutic response when adoptively transferred, Applicant offers that several cell types, including CTLs, tumour infiltrating lymphocytes (TILs), natural killer (NK) cells, and T-helper cells, were known at the time of filing of the present application to be capable of effecting a therapeutic response when adoptively transferred. Moreover, Applicant asserts that each of these cell types is capable of acting as an effector cell when transduced or transfected with a nucleic acid sequence encoding a chimeric receptor of the invention, wherein expression of the chimeric receptor confers upon an effector cell the ability to become activated in response to bound ligand recognized by the extracellular ligand association domains of the chimeric receptor. Thus, each of these effector cell types is a good candidate for *ex vivo* transduction or transfection with a novel nucleic acid of the invention, followed by adoptive transfer. The Hwu et al. reference further corroborates this statement, minimally with regard to TILs, as it is directed to the use of *ex vivo* transduced TILs in adoptive transfer experiments wherein the transduced TILs target human ovarian cancer cells for destruction.

Regarding the practice of *in vivo* or *ex vivo* gene therapy, which the Examiner views as constituting highly unpredictable arts that require undue experimentation, Applicant offers that the claims are directed to a novel nucleic acid sequence encoding a chimeric receptor, rather than a method of using same for *in vivo* or *ex vivo* gene therapy. All that is required to satisfy the

enablement requirement is one credible use. Applicant asserts that this requirement is more than satisfied by the specification. A skilled practitioner having read the specification would, therefore, envision a plurality of uses for a nucleic acid sequence encoding a novel chimeric receptor of the invention. Two credible uses involving adoptive transfer of CD4+ T cells and adoptive transfer of CD8+ T cells are described below for the Examiner's consideration.

The present application clearly demonstrates the functional expression of a chimeric receptor as claimed in Jurkat cells, a human CD4+ T cell line. See instant Examples. When stimulated by antigen, the chimeric receptor effectively induces downstream signaling resulting in activation of the T cells, as demonstrated by expression of IL-2. See Figures 4 and 5. The induction of IL-2 expression is described in the Examples, and is understood in the art, to be a marker of T cell activation. IL-2 is one of many cytokines produced by activated T cells which function to orchestrate immune responses.

The Examples, therefore, render it apparent that the claimed chimeric receptors are capable of activating CD4+ T cells. Accordingly, one credible use for the chimeric receptors of the invention is the transfection and adoptive transfer of CD4+ T cells. CD4+ T cells (or T-helper cells) are one of the effector cell types listed in the application at page 9, line 19. Moreover, it was well known at the time of filing of the present application that activated T-helper cells are able to promote an immune response which leads to the destruction of antigen-presenting target cells. For example, the ability of antigen-specific T-helper cells to promote antigen-specific anti-tumor responses following adoptive transfer was known in the art at the time of the invention. See Bookman et al., 1987, J. Immunol. 139:3166-3170; IDS Reference AM).

Furthermore, a skilled practitioner would anticipate that the chimeric receptors of the present invention, which were demonstrated to activate Jurkat cells (CD4+ T cells), would also be capable of activating CTLs. Such a skilled practitioner would base this expectation, at least in part, on the findings of the present inventors, which had already revealed that the ability of chimeric receptors to activate Jurkat cells is predictive of their ability to activate CTLs. See WO 97/23613; IDS Reference AN. In Example 3 of WO 97/23613 (beginning at page 28, line 1), a chimeric receptor expressed in Jurkat cells is shown to be capable of activating these cells in response to cellular antigen, as measured by IL-2 release. In Example 6 of WO 97/23613 (starting at page 34, line 25), CTLs expressing the same chimeric receptor (P67.6/G1/TCR zeta)

were shown to be capable of causing antigen-targeted cell lysis (Figure 20). Thus, the inventors had already established that chimeric receptor-mediated activation of Jurkat cells was a useful predictive model for chimeric receptor-mediated CTL activation and associated antigen-specific target cell lysis.

Moreover, as indicated above, the *in vivo* efficacy of CTLs transfected *ex vivo* with a chimeric receptor and subsequently adoptively transferred was already established at the time of the invention. See, for example, Moritz et al. (1994, Proc. Natl. Acad. Sci. 91:4318-4322), Hwu et al. (1995, Cancer Res. 55:3369-3373), and Hekele et al. (1996, Int. J. Cancer 68:232-238). The authors of these references established the cytolytic activity of the CTLs *in vitro* and then extended these results to confirm their activity *in vivo*. See Moritz et al., Abstract and page 4321, Figure 4; Hwu et al., Abstract and page 3369, right hand column, first full paragraph, last sentence; and Hekele et al., Abstract, page 236, left column, first full paragraph, and Figures 3 and 4). Indeed, the Examiner appears to recognize that CTLs are capable on their own of effecting a therapeutic response.

A skilled practitioner having an awareness of the above findings, would have every expectation that the chimeric receptors of the present invention, which are shown to activate Jurkat cells *in vitro*, would also activate CTLs *in vitro* and would, in turn, be effective *in vivo*.

In view of the support presented in the specification and available in the art at the time of filing, and arguments presented herein, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection of claims 34-38 under 35 U.S.C. § 112, first paragraph.

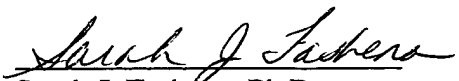
Fees

No additional fees are believed to be necessitated by this amendment. However, should this be an error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted, therefore, that the claims are in condition for allowance. No new matter has been introduced. Allowance of all claims at an early date is solicited. In the event that there are any questions concerning this amendment, or application in general, the Examiner is respectfully urged to telephone the undersigned so that prosecution of this application may be expedited.

Respectfully submitted,



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Enclosures: Petition for a Three-Month Extension of Time
Supplemental Information Disclosure Statement